DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 1998D–0834 (formerly Docket No. 98D–0834]

Draft Guidance for Industry on Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms—Recommended Prescribing Information for Health Care Providers and Patient Labeling; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms—Recommended Prescribing Information for Health Care Providers and Patient Labeling." The draft guidance is intended to assist applicants in developing labeling for new drug applications (NDAs) for such drug products. This is the fifth draft of the guidance, which FDA initially published for comment in October 1998.

DATES: Submit written or electronic comments on the draft guidance by [*insert date 60 days after date of publication in the* **Federal Register**]. General comments on agency guidance documents are welcome at any time.

ADDRESSES: Submit written requests for single copies of the draft guidance to the Division of Drug Information (HFD–240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing

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your requests. Submit written comments on the draft guidance to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments*. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Margaret Kober, Center for Drug Evaluation and Research (5359), Food and Drug Administration, 10903 New Hampshire Ave., bldg. 22, rm. 5376, Silver Spring, MD 20993, 301–796–0934.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance entitled "Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms—Recommended Prescribing Information for Health Care Providers and Patient Labeling." The draft guidance describes the recommended labeling for health care providers and patient instructions for inclusion in NDAs.

A draft of this guidance was first issued on October 15, 1998 (63 FR 55399). After public review and comment, a second version of this draft guidance was issued on September 27, 1999 (64 FR 52100). On May 31, 2002, the National Institutes of Health Women's Health Initiative (WHI) study of oral conjugated estrogens (CE 0.625 milligram (mg)) plus medroxyprogesterone acetate (MPA 2.5 mg)/day in postmenopausal women was stopped after a mean of 5.2 years of followup because test statistics for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. Data on the major clinical outcomes regarding increased risks for invasive breast cancer, heart attacks,

strokes, and venous thromboembolism rates, including pulmonary embolism, became available July 17, 2002. Consequently, the agency withdrew the draft guidance on September 10, 2002 (67 FR 57432), pending consideration of the results from the WHI study. In the **Federal Register** of February 3, 2003 (68 FR 5300), the agency issued a third draft reflecting the agency's thinking after consideration of the results from the WHI study concerning overall risks and benefits of hormone therapy for postmenopausal symptoms.

A fourth draft of this guidance was issued on February 17, 2004 (69 FR 7492), to address comments received, incorporate new study results from the Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI study, and better inform prescribers and patients regarding the availability of the lowest effective dose for these drug products. (The results of the WHIMS substudy were published on May 28, 2003. Postmenopausal women, 65 to 79 years of age, during 4 years of treatment with CE 0.625 mg plus MPA 2.5 mg/day had a greater risk of developing probable dementia than those on placebo.)

The agency is issuing this fifth draft of the guidance to incorporate new study results from the WHI and WHIMS studies. This fifth draft supersedes the fourth draft, and retains and updates the labeling recommendations regarding the results of the WHI study and the WHIMS substudy for postmenopausal women treated with CE 0.625 mg plus MPA 2.5 mg/day. It also reflects the agency's thinking after consideration of the results published on April 14, 2004, of the WHI study, and the results published on June 23/30, 2004, of the WHIMS substudy for postmenopausal women with prior hysterectomy treated with CE 0.625 mg/day alone. The WHI study of CE 0.625 mg/day alone in postmenopausal women with prior hysterectomy was stopped after a mean followup of 6.8 years because of an increased risk of stroke. The

WHIMS substudy of CE 0.625 mg/day alone was stopped after a mean followup of 5.2 years. Estrogen-alone therapy did not reduce probable dementia or cognitive decline incidence and increased the risk for both endpoints combined. This fifth draft of the guidance recommends adding risk information related to the results of the WHI and WHIMS estrogen-alone studies to appropriate sections of labeling including the boxed warning. Further revisions to the guidance may be necessary as additional information becomes available.

This level 1 draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the agency's current thinking on labeling for noncontraceptive estrogen drug products for the treatment of moderate to severe vasomotor symptoms and moderate to severe vulvar and vaginal atrophy symptoms. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

II. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guidance and received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

III. Electronic Access

Persons with access to the Internet may obtain the document at either *http://www.fda.gov/cder/guidance/index.htm* or *http://www.fda.gov/ohrms/dockets/default.htm.*

Dated: 11/8/05
November 8, 2005.

Jeffrey Shuren,
Assistant Commissioner for Policy.

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